Renal and neurohumoral effects of dopamine and oral dopamine agonists

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SUMMARY AND CONCLUSIONS

Over the last few years considerable changes have occurred in the concepts about pharmacological treatment of congestive heart failure (CHF). In the sixties diuretics (and digoxine) had been mainly used, whereas since the seventies the field had long been dominated by the haemodynamic concept, stressing the importance of vasodilation.

Because vasoconstriction is present in CHF, vasodilators were introduced. Reduction of pre- and afterload seemed beneficial for patients with CHF. Indeed in 1986 the V-HeFT (I) study showed that treatment with hydralazine combined with isosorbide dinitrate resulted in a reduction in mortality in patients with CHF. However, in the same study, prazosin, an even more potent vasodilator, had an adverse effect. Another class of drugs, the phosphodiesterase inhibitors, which were initially considered as promising drugs in the treatment of CHF thanks to their favorable hemodynamic profile: they combine vasodilating properties with positive inotropic effects, showed a considerable increase in mortality in longterm studies, for example the PROMISE study with milrinone. One of the factors that may contribute to this adverse effect is neurohumoral activation.

Late in the eighties it appeared that ACE inhibitors (ACEI), drugs that combine favorable haemodynamic effects with a decrease in neurohumoral activation, not only reduced symptoms in patients with CHF, but also could improve survival. They now have become the cornerstone in the treatment of CHF. ACEI have an inhibitory effect not only on the renin-angiotensin-aldosterone-system (RAAS), but also on the sympathetic nervous system (SNS). Beta blockers, which sometimes have adverse effects during acute CHF, may improve exercise tolerance and perhaps survival during chronic treatment of CHF. Thus, the hemodynamic hypothesis has lost ground to the so-called neurohumoral concept, which states that during chronic treatment of CHF an inhibitory effect of the RAAS and SNS may be more important than the hemodynamic effect.

In the light of this shift in paradigmas of CHF treatment, it is interesting to see comparable developments in the use of dopamine and dopamine agonists. Dopamine gained its place in the intensive care setting and in the acute treatment of CHF, because of haemodynamic (and natriuretic) effects. Later, positive effects of long term treatment of CHF were reported with oral levodopa.

Expectations were high when an orally active, selective DA-1 dopamine agonist, fenoldopam, was developed. Hemodynamic effects in acute studies were indeed impressive. However, its use in chronic treatment of hypertension and CHF proved to be disappointing. This is supposed to be related to activation of the SNS and RAAS, not only as a compensatory response to the vasodilation, but even due to a direct stimulating effect on renin release. On the other hand, with the hemodynamically weaker and aselective orally active dopamine agonist, ibopamine, positive results on exercise tolerance during chronic treatment of CHF were found (DIMT study). In acute studies a fall in plasma norepinephrine levels an a neutral or diminishing effect on the RAAS were observed.

This was the situation before the start of the studies described in this thesis. We investigated not only the hemodynamic effects, but also whether the increase in renal plasma flow (ERPF) and glomerular filtration rate (GFR), observed in patients with congestive heart failure (CHF) during treatment with ibopamine, are due to specific renal hemodynamic effects or to systemic hemodynamic effects (chapter 3). We appreciated, that
ibopamine caused a small but significant increase in both ERPF and GFR. However, ibopamine increased cardiac output and decreased systemic vascular resistance to a similar extent and we found no change in the ratio renal blood flow / cardiac output. Therefore, the renal effects of ibopamine with equal pre- and postglomerular vasodilation, appear to be primarily due to its systemic hemodynamic effects. We also investigated in this study whether the acute renal effects during treatment with ibopamine were also present after longterm treatment. Acute on chronic administration of ibopamine also increased both ERPF and GFR. The increase of ERPF after the acute on chronic administration of ibopamine was less pronounced compared to the increase in ERPF after the acute administration of ibopamine. No signs of tolerance were observed with respect to the response of GFR during prolonged treatment with ibopamine. Furthermore in none of the patients a deterioration of renal function was observed during prolonged treatment with ibopamine. Apart from these renal and systemic hemodynamic effects we investigated the acute and chronic neurohumoral effects of ibopamine treatment in these patients with mild CHF. We observed that plasma renin activity (PRA) and plasma aldosterone remained unchanged. However the acute administration of ibopamine lowered plasma norepinephrine levels and these levels remained unchanged after the acute on chronic administration of ibopamine.

Nowadays, ACEI are the cornerstone in the treatment of congestive heart failure and also in the treatment of diabetic nephropathy and nephrotic syndrome. Many renal hemodynamic and neurohumoral effects are shared by angiotensin converting enzyme inhibitors (ACEI) and dopamine, while their mode of action is quite different. The combination of ACEI and dopamine might have more pronounced and perhaps favorable neurohumoral and renal effects. In chapter 4 we investigated therefore the effects of addition of dopamine to an angiotensin converting enzyme inhibitors (ACEI) in healthy volunteers. We observed that the addition of dopamine infusion to ACE-inhibition enhances renal vasodilation probably by pre- but predominantly postglomerular vasodilation, reflected by an increase in ERPF and a decrease in FF, without a change in GFR. Furthermore, it promotes natriuresis without changing the renin angiotensin aldosterone system (RAAS) or plasma norepinephrine levels in healthy volunteers. Therefore studies in diseases like congestive heart failure, diabetic nephropathy and nephrotic syndrome not only with the combination of ACEI with dopamine, but also with orally available dopamine agonists are needed. They might not only show favorable renal effects, but perhaps also a decrease in neurohumoral parameters.

As stated previously, much attention has been paid to neurohumoral effects in patients with CHF. Especially plasma norepinephrine levels, as a reflection of sympathetic nervous system activation, are correlated to the mortality rate in patients with CHF. Therefore drugs that may decrease plasma norepinephrine levels could be of additional value in the treatment of CHF. Presynaptic DA-2 dopaminergic and α-2 adrenergic receptor stimulation in vitro decreases plasma norepinephrine levels.

In chapter 5 we used a standardised exercise test as a model for sympathetic stimulation in normal man and investigated whether dopamine in different doses alone or in combination with a DA-2 dopamine receptor antagonist, domperidone, influenced plasma renin activity and plasma aldosterone. The acute effects of dopamine on plasma renin activity and aldosterone release were consistent with the inhibitory effect of dopamine on aldosterone release during sympathetic stimulation. However, the acute effects of dopamine on plasma renin activity and aldosterone release during sympathetic stimulation were not abolished by the DA-2 dopamine receptor antagonist, domperidone. The finding that an increase in plasma renin activity in venous plasma during sympathetic stimulation was not abolished by domperidone, supports the view that dopamine exerts a sympatholytic effect on plasma renin activity independently of its actions on the renin angiotensin aldosterone system. Therefore studies in diseases like congestive heart failure, diabetic nephropathy and nephrotic syndrome not only with the combination of ACEI with dopamine, but also with orally available dopamine agonists are needed. They might not only show favorable renal effects, but perhaps also a decrease in neurohumoral parameters.

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plasma norepinephrine levels. Dopamine 1 μg/kg/min infusion blunted the increase in plasma norepinephrine levels during graded exercise compared to either placebo or dopamine 3 μg/kg/min infusion. We presume that for this dose of dopamine the inhibitory effects of presynaptic DA-2 dopamine or α-2 adrenoceptor stimulation on norepinephrine release predominate. When dopamine is infused at a higher dose, 3 μg/kg/min, the inhibitory effects might be counteracted by uptake-1 inhibition or enhanced synthesis and release of norepinephrine by dopamine. The increase in plasma norepinephrine levels during graded exercise is augmented during infusion of dopamine combined with domperidone, which further supports the theory that DA-2 dopaminergic receptor stimulation is important in the control of plasma norepinephrine levels. One might argue that an increase in arm flow during exercise plus dopamine might also lead to such a fall in venous plasma norepinephrine levels.

Therefore we used (chapter 5) a cold pressor test as a stimulus for the sympathetic nervous system in a comparable study protocol as for the exercise test (chapter 6). A cold pressor test will result in vasoconstriction and a fall in blood flow even in the contralateral arm, in contrast to an exercise test. We observed that in healthy volunteers dopamine 1 μg/kg/min infusion blunts the increase in plasma norepinephrine levels during a cold pressor test compared to either placebo or dopamine 3 μg/kg/min infusion. The addition of domperidone abolished the lowering effect of dopamine 1 μg/kg/min, whereas the addition of domperidone had no effect on dopamine 3 μg/kg/min. These results support that only a low dose of dopamine (1 μg/kg/min) might decrease plasma norepinephrine levels in an activated sympathetic nervous system and that these effects are probably not due to an increase in blood flow.

Dopamine is in general use in the intensive care unit or perioperatively. Low dose dopamine, 1-4 μg/kg/min, is usually given with the intention to maintain diuresis and possibly renal function. However, whether renal function is influenced by dopamine during mechanical ventilation with PEEP is not known yet, although it is nearly always given for this reason.

In chapter 7 we showed that dopamine in doses up to 4 μg/kg/min increases renal blood flow (RBF) and GFR in a dose dependent way in these patients. However, the increase in RBF can fully be ascribed to the increase in cardiac output. At a dose of 8 μg/kg/min, dopamine even decreases the fraction of the cardiac output directed to the kidneys. Diuresis and natriuresis are increased by dopamine in a dose dependent way for all the doses used, and therefore probably independent of the renal hemodynamic effects. So, when the goal is to obtain a maximal increase in RBF and GFR, with an additional increase in diuresis and sodium excretion, dopamine in a dose of 4 μg/kg/min should be given. However, whether dopamine in a low dose may preserve renal function in these and other patients, is still a matter of debate.